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Blanc et al. (Clinical Therapeutics, 1998), 20(5), 901-912)  
Foidart, J.M., British J. of Obstetrics and Gynecology, (1997), 104(3), 305-310.  
Conard et al., Fertil. Steril. (64, No. 5, 957-62, (1995). complete article.  
De Leo, V. et al., Maturitas, (1999), 31(20, 171-177.

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Article title	Comparison of two HRT regimens with bimonthly and monthly progestin administration in postmenopause
Article identifier	0378512299000110
Authors	De_Leo_V La_Marca_A Morgante_G Lanzetta_D
Journal title	Maturitas
ISSN	0378-5122
Publisher	Elsevier Ireland
Year of publication	1999
Volume	31
Issue	2
Supplement	0
Page range	171-177
Number of pages	7
User name	Adonis
Cost centre	
PCC	\$22.00
Date and time	Monday, February 24, 2003 9:02:54 PM

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## Comparison of two HRT regimens with bimonthly and monthly progestin administration in postmenopause

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Received 20 April 1998; received in revised form 26 June 1998; accepted 6 July 1998

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### Abstract

**Objectives:** Here we report the results of a study in which natural estrogens were given transdermally cyclically and continuously for 1 year, and a progestin of the latest generation, namely nomegestrol acetate, was given for 10 days every month and for 15 days every 2 months. **Methods:** The patients were a group of 34 post-menopausal women (51–56 years), 18 of whom (group A) were treated with continuous transdermal estradiol (50 µg/day) and cyclic oral nomegestrol at a dose of 5 mg/day for 15 days every 2 months for 1 year. The other 16 women (group B) were treated with cyclic transdermal estradiol for 3 weeks with oral nomegestrol for 10 days (12–21)/month. Endometrial thickness was evaluated by transvaginal ultrasonography before and after treatment. At the end of treatment, an endometrial biopsy was performed. Serum total cholesterol, HDL, LDL and triglycerides were assessed at baseline and every 4 months. The characteristics of the cycle were deduced from the diary cards recorded by the women. **Results:** No significant differences were found in the mean interval between the last dose of nomegestrol and the start of bleeding or in the duration of bleeding. The total number of days of bleeding per year was significantly lower in group A than group B ( $27 \pm 12$  vs  $52 \pm 18$ ;  $P < 0.01$ ). Total serum cholesterol and LDL significantly decreased after 1 year of treatment in both groups, HDL-cholesterol and triglycerides were found increased at most of the time points studied. **Conclusions:** The present protocol involving continuous transdermal administration of estrogen combined with oral progestin every 2 months gave good control of the menstrual cycle, did not increase the risk of endometrial pathology and met with good patient compliance. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Postmenopausal women; HRT; Transdermic natural estrogens; Nomegestrol acetate; Lipids; Bimonthly progestin administration

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### 1. Introduction

It has been known for more than 20 years that estrogen-replacement therapy (ERT) without

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progesterone is associated with increased risk of endometrial hyperplasia and adenocarcinoma. The relative risk in unopposed ERT is reported to range from 0.9 to 12 [1,2]. A recent meta-analysis found a risk of 2.3, which was higher in women using higher doses of estrogen and was related to the duration of ERT [3]. The relative risk of endometrial carcinoma in combined ERT was also calculated in the same meta-analysis, and was 0.8; this figure did not differ in a statistically significant way from that of the general population.

With HRT used in the last 20 years, researchers have demonstrated that the protective effect of progesterone depends on dose, and especially on the number of days of administration [4,5]. On the basis of current understanding, it seems that 10–14 days of progesterone administration per treatment cycle are necessary, whereas the actual dose of progesterone is less important. In order to prevent endometrial hyperplasia, it is not necessary to obtain secretory transformation of the endometrium but only a balance between estrogen and progesterone sufficient to reduce mitotic activity [6].

In Europe, sequential HRT protocols involving progesterone administration for at least 10 days/month, are the most widely used. In most women such protocols induce regular pseudo-menstrual bleeding but in some cases also spotting. Some women view suspension of bleeding as an unwanted side-effect of therapy, and for many of them it is one of the main reasons for low compliance towards HRT.

New preparations based on natural estrogens such as  $17\beta$ -estradiol at low doses have made many alternative protocols possible. These protocols make therapy more acceptable to women without reducing the benefits. The protective effects on the endometrium of HRT with progesterone given less than once per month are still in part unknown. The present study reports the effects on endometrial histology, bleeding patterns and circulating lipids of a protocol, involving continuous transdermal administration of natural estrogen and cyclic oral administration of norgestrel acetate for 15 days every 2 months.

Norgestrel acetate is a derivative of 19-norprogesterone and is one of the latest progestins

with oral efficacy. Its affinity for endometrial progesterone receptors has been demonstrated by its capacity to induce secretory transformation of the uterine mucosa at a dose of 5 mg/day.

## 2. Materials and methods

### 2.1. Patients

The subjects were 34 women, 51–56 years of age, in physiological menopause for from 6 months to 4 years. Menopausal status was confirmed by plasma levels of FSH  $> 50$  mIU/ml and of estradiol  $< 30$  pg/ml. No woman had taken hormones in the year preceding the study. Routine blood chemistry was performed together with Papanicolaou smear, Vabra endometrial biopsy and mammography to exclude the presence of pathology. Body mass index (BMI) was between 24 and 26 kg/m<sup>2</sup>. After initial evaluation, the patients were assigned to one of two treatment protocols by means of a random number table. One protocol involved continuous transdermal administration of  $17\beta$ -estradiol (50  $\mu$ g/day Dermestril 50, Rotapharm, Monza, Milan) and cyclic oral administration of norgestrel (Lutenyl, Schering, Milan) at a dose of 5 mg/day for 15 days, every 60 days from day 45 until day 60, for a year (group A,  $n = 18$ ); the other involved cyclic transdermal administration of estradiol for 3 weeks and oral administration of norgestrel at a dose of 5 mg/day for 10 days/month (from 12 to 21) (group B,  $n = 16$ ).

### 2.2. Ultrasonography

Transvaginal ultrasonographic examination was performed with a 3.5–5-MHz probe (Sonoline, Siemens, Milan) before and after the study period. Endometrial thickness was evaluated at both examinations

### 2.3. Endometrial histology

In the twelfth month of the protocol, between days 52 and 55 for group A and between days 18 and 21 for group B, a second Vabra endometrial

biopsy was performed. Specimens were fixed in formalin and stained with haematoxylin–eosin. Histological assessment was performed by a single pathologist.

#### 2.4. Vaginal bleeding.

Vaginal bleeding was recorded on daily diary cards. The number of days between the last progesterone pill and the start of suspension bleeding was recorded, together with the duration and quantity of bleeding. The characteristics of the cycle were deduced from the diaries. Bleeding was evaluated subjectively using a scoring system from 0 to 4 in which 0 indicated absence of bleeding, 1 spotting, and 2, 3 and 4 slight, moderate and heavy bleeding, respectively.

#### 2.5. Circulating lipids.

Serum cholesterol, triglycerides, HDL- and LDL-cholesterol (calculated using the Friedewald's formula) were assessed at baseline and every 4 months on days 46 and 60 of treatment for group A and on days 12 and 21 for group B.

#### 2.6. Statistical analysis

The results were expressed as means and standard deviations. Statistical analysis was performed by the *t*-test for paired and unpaired data. Statistical significance was set at  $P < 0.05$ .

### 3. Results

The two groups of patients did not differ in mean age, BMI or age at menopause (Table 1). Two women in group A and one in group B left the study, two because of severe uterine bleeding and one because of headache. Of the 34 initial endometrial biopsies, eight indicated proliferative endometrium and 26 atrophic endometrium. The biopsy performed after 1 year of treatment showed nine cases of late secretory endometrium and seven of early secretory endometrium in group A, and 11 cases of late secretory and four of early secretory endometrium in group B (Table

2). Transvaginal ultrasonography before and after treatment, respectively, showed mean endometrial thicknesses of  $3.8 \pm 1.8$  and  $6.3 \pm 1.6$  mm in group A and of  $3.6 \pm 1$  and  $5.6 \pm 1.6$  mm in group B, respectively.

Three women in group A and two in group B complained of spotting or light bleeding during the first cycle of therapy only. In the women of group A given nomegestrol for 15 days every 60 days, bleeding occurred every 9–10 weeks, 7–8 days after the last nomegestrol pill. In the women (group B) given nomegestrol for 10 days every month bleeding usually occurred 5–7 days after the last nomegestrol pill. Table 3 gives all characteristics of vaginal bleeding in both groups. No significant differences were found in the mean interval between the last dose of nomegestrol and the start of bleeding or in the duration of bleeding. In the women of group A the total intensity of bleeding at 10 and 12 months was significantly higher ( $P < 0.05$ ) than at 2, 4 and 6 months of therapy. The total number of days of bleeding was significantly lower in group A than group B ( $27 \pm 12$  vs  $52 \pm 18$ ;  $P < 0.01$ ).

Baseline levels of serum cholesterol, triglycerides, HDL- and LDL-cholesterol were similar in the two groups. Serum cholesterol concentrations fell by 4.5% in group B ( $P < 0.05$ ) and by 3.4% in group A ( $P < 0.05$ ) (Fig. 1). HDL concentrations did not change significantly after 1 year of treatment in both groups; however, significant increases ( $P < 0.05$ ) from baseline were observed at the second month for group B (4.5%) and at the eighth (6%) months for group A (Fig. 2). For triglycerides, significant increases ( $P < 0.05$ ) from baseline were observed in both groups at most of the time points studied (Fig. 3). LDL concentra-

Table 1  
Demographic comparison before HRT

	Group A (n = 18)	Group B (n = 16)
Age (years)	$53 \pm 1$	$53 \pm 2$
BMI (kg/m <sup>2</sup> )	$25 \pm 0.8$	$24.8 \pm 0.6$
Age at menopause (years)	$49 \pm 1.4$	$50 \pm 1.2$

Values are mean  $\pm$  S.D.

Table 2  
Endometrial histology before and after 12 months of HRT

Histological diagnosis	Group A		Group B	
	Before (n = 18)	After (n = 16)	Before (n = 16)	After (n = 15)
Insufficient tissue	0	0	0	0
Atrophic	15	0	11	0
Proliferative	3	0	5	0
Early secretory	0	7	0	4
Late secretory	0	9	0	11
Hyperplastic	0	0	0	0

tions significantly decreased ( $P < 0.05$ ) from baseline in both groups at most of the time points studied (Fig. 4). The LDL/HDL ratio fell by 10% in both groups ( $P < 0.01$ ).

#### 4. Discussion

The results show that the present protocol involving continuous transdermal administration of estrogen combined with oral progesterone every 60 days gave good control of the menstrual cycle, did not increase the risk of endometrial pathology and met with good patient compliance. Suspension bleeding occurred 7–8 days after the last progesterone pill and lasted  $5 \pm 2$  days, which is only slightly longer than the duration observed for sequential protocols with progesterone given monthly.

A reduction in the number of pseudo-menstruations per year during HRT is certainly of interest for women who do not wish to have monthly bleeding. From the safety viewpoint, the ultrasound and endometrial biopsy data, though obtained in a limited number of cases, indicates that administration of progesterone for 15 days every 2 months provides good control of endometrial development. Previous studies have shown that administration of progesterone for 7 days/month reduces the incidence of endometrial hyperplasia by 4% in comparison to unopposed estrogen therapy [7].

The protective effect of progesterone is largely linked to a reduction in estrogen receptors, transformation of estradiol to estrone and a reduction

in DNA synthesis in the endometrium [8,9]. The administration of a progesterone such as norgestrel acetate at the dose used in this study, seems to produce the above effects and can therefore be presumed to protect the endometrium. It should be recalled that transdermal estrogen therapy at a dose of 50  $\mu\text{g/day}$  produces plasma levels of estradiol of 40–45 pg/ml, which match those of healthy women of reproductive age in the first days of the cycle, when estrogen concentrations are lowest.

Like endometrial biopsy, transvaginal ultrasound examination also provided useful information on endometrial status [10].

Regarding menstrual bleeding, the women who received norgestrel every 60 days bled every 2 months, compared to monthly bleeding in those who received it every 28 days. In group A menstrual bleeding occurred 7–8 days after the last norgestrel pill, a longer interval than with other progestins. This may be because norgestrel induces slow endometrial transformation in secretory phase. The women of group A have the advantage of half the number of pseudo-menstrual bleedings and premenstrual symptoms per year. Basal histological examination of endometrial specimens showed atrophic endometrium in both groups. At the end of 1 year of HRT secretory transformation occurred in the majority of women in both groups. This is presumably because the endometrial biopsy was performed during progestin administration. Our results are in agreement with previous studies [11,12] in which full secretory transformation is said to be required for endometrial protection. In our study we did

Table 3

Bleeding patterns in women receiving norgestrel for 15 days every 2 months (group A;  $n = 16$ ) and norgestrel for 10 days every month (group B;  $n = 15$ )

	Months					
	2	4	6	8	10	12
<b>Group A</b>						
Interval	$9 \pm 2$	$8 \pm 4$	$8 \pm 3$	$7 \pm 3$	$7 \pm 2$	$7 \pm 2$
Duration	$4 \pm 2$	$4 \pm 2$	$4 \pm 3$	$5 \pm 1$	$5 \pm 2$	$5 \pm 2$
Total intensity	$9.6 \pm 0.8$	$9.2 \pm 0.1$	$8.8 \pm 0.9$	$12 \pm 1$	$13.5 \pm 0.8^*$	$14 \pm 1.2^*$
Mean intensity	$2.4 \pm 0.6$	$2.3 \pm 0.6$	$2.2 \pm 0.7$	$2.4 \pm 0.6$	$2.7 \pm 0.3$	$2.8 \pm 0.7$
<b>Group B</b>						
Interval	$6 \pm 2$	$5 \pm 2$	$4 \pm 3$	$4 \pm 3$	$4 \pm 2$	$4 \pm 2$
Duration	$5 \pm 3$	$5 \pm 3$	$5 \pm 2$	$4 \pm 3$	$4 \pm 1$	$4 \pm 1$
Total intensity	$11 \pm 0.4$	$12 \pm 0.7$	$11.5 \pm 0.7$	$10 \pm 0.6$	$9.2 \pm 0.6$	$9.6 \pm 0.6$
Mean intensity	$2.2 \pm 0.3$	$2.4 \pm 0.4$	$2.3 \pm 0.4$	$2.5 \pm 0.2$	$2.3 \pm 0.3$	$2.4 \pm 0.4$

Values are mean  $\pm$  S.D.

\* $P < 0.05$  vs 2, 4 and 6 months of therapy.

not find any case of endometrial hyperplasia in either group; this suggests that progestin administration for 15 days every 60 days is a safe protocol. Nevertheless, the number of patients is rather small for drawing negative conclusions.

Estrogen replacement therapy has been shown to reduce the risk of coronary disease [13]. The most probable mechanism of this effect is the modification of lipid profiles [14]. Transdermal estradiol therapy is reported to decrease serum triglycerides and total, LDL- and HDL-cholesterol [15]. Another study reported no effect of transdermal estradiol on serum HDL levels [16]. For transdermal estradiol therapy, a protective effect on the risk for coronary disease has not yet been demonstrated. The administration of a progestin to protect the endometrium reduces the positive effects of estradiol on lipid profiles. However, this reduction depends on dose and the androgenicity of the progestin [17]. It has been shown that norgestrel does not alter lipid or glucose metabolism and no reduction in HDL-cholesterol has been reported [18]. Other studies have shown that norgestrel has antiandrogenic properties [19].

The results of our study show that protocols with transdermal estradiol and norgestrel have

favourable effects on serum lipids. Changes in plasma levels of cholesterol, HDL, LDL, and triglycerides were not significantly different in the two groups, while HDL plasma levels were found to be significantly increased from baseline at the fourth and eighth months for group A and only at the second month for group B. However, the LDL/HDL ratio was reduced by 10% in both groups after 1 year of treatment. This reduction was significant after 4 months of therapy for group A and after 10 months of therapy for group B.

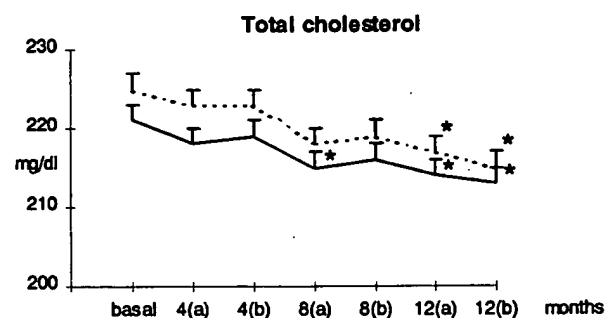


Fig. 1. Serum total cholesterol were assessed at baseline and every 4 months on days 46 (a) and 60 (b) of treatment for group A (—) and on days 12 (a) and 21 (b) for group B (---). \*Statistically significant difference ( $P < 0.05$ ) from baseline. Values are means  $\pm$  S.D.

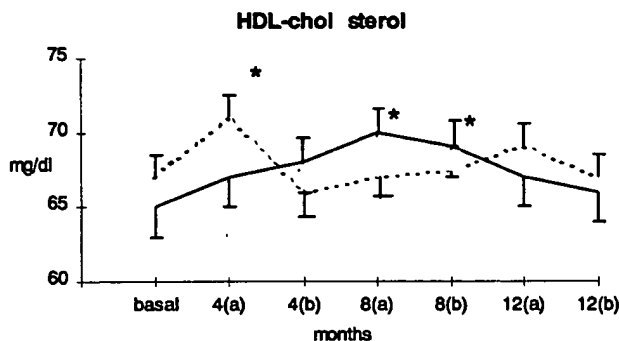


Fig. 2. Serum HDL-cholesterol were assessed at baseline and every 4 months on days 46 (a) and 60 (b) of treatment for group A (—) and on days 12 (a) and 21 (b) for group B (---). \*Statistically significant difference ( $P < 0.05$ ) from baseline. Values are means  $\pm$  S.D.

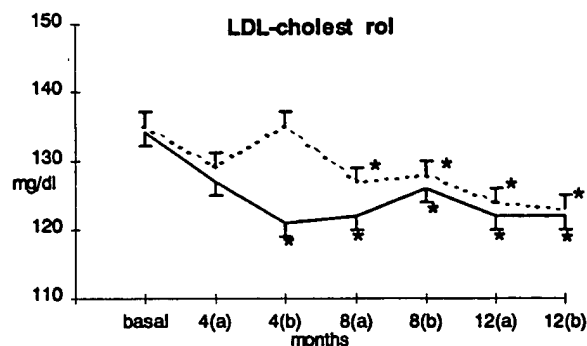


Fig. 4. Serum LDL-cholesterol were assessed at baseline and every 4 months on days 46 (a) and 60 (b) of treatment for group A (—) and on days 12 (a) and 21 (b) for group B (---). \*Statistically significant difference ( $P < 0.05$ ) from baseline. Values are means  $\pm$  S.D.

In conclusion, the present results show that in postmenopause, one year of HRT with 50  $\mu$ g/day natural estrogen and 5 mg noregestrol acetate for 15 days every 60 days may protect the endometrium against hyperplasia and other pathologies, and has the advantage of making HRT more acceptable to women. The protocol was found to have favourable effects on serum lipids. Because of the small number of the patients in both groups, other studies including a larger number are requested.

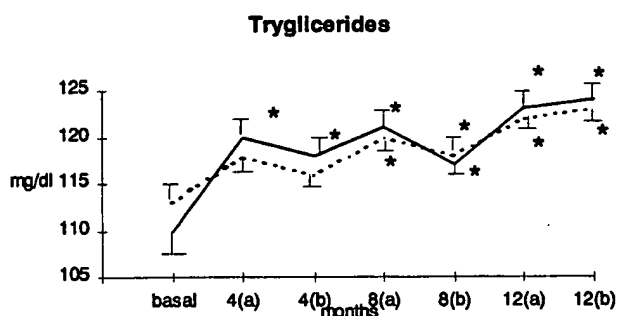


Fig. 3. Serum triglycerides were assessed at baseline and every 4 months on days 46 (a) and 60 (b) of treatment for group A (—) and on days 12 (a) and 21 (b) for group B (---). \*Statistically significant difference ( $P < 0.05$ ) from baseline. Values are means  $\pm$  S.D.

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